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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,278	11/05/2001	Sydney David Finkelstein	FINKEL-1 CONT II	2727

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Ansel M. Schwartz
Suite 304
201 N. Craig Street
Pittsburgh, PA 15213

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,278	FINKELSTEIN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0703* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed June 19, 2003. Currently, claims 18-35 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Priority

3. This application claims priority to 08/667,493, filed June 24, 1996 and 08/311,553, filed September 23, 1994.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Response to Arguments

The response traverses the rejection. The response asserts the priority data has been amended, however, there do not appear to be any amendments to the specification in the instant response.

Specification

4. On page 22, line 7, the specification recites "cite?". It is unclear whether there is a cite missing from the disclosure or whether this recitation is in error. Applicant is reminded that no new matter may be added.

Response to Arguments

The response traverses the rejection. The response asserts the specification has been amended, however, there do not appear to be any amendments to the specification in the instant response.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 18-32, 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Meltzer et al (PNAS, Vol. 88, pages 4976-4980, June 1991).

Meltzer et al. (herein referred to as Meltzer) teaches a method of detecting LOH using PCR. Meltzer modified the PCR reaction to enable detection of LOH using small quantities of DNA obtained from microdissected frozen biopsies or archival paraffin sections (page 4976, col. 2). Meltzer teaches a genotyping method comprising obtaining a specimen of cells containing DNA and placing under a microscope, inspecting the cells to determine target cells, choosing target ells based on morphological features characteristic of a disease and separating the target cells (page 4976, col. 2, para 2) by teaching that cell samples were obtained from patients with esophageal cancer frozen in liquid nitrogen, embedded in paraffin and microdissected

by placing the sample under the microscope and observing morphological differences between the tumor areas and normal cells (limitations of Claims 18 a, b, c, d, 19-22). Meltzer then teaches that the tumor cells were microdissected to separate them from adjacent normal cells to achieve an enrichment of about 70% or greater. Meltzer then places the separated piece into a container, centrifuging to make a pellet and withdrawing supernatant to obtain DNA (page 4976, col. 2, para 3) by teaching that the separated tissue was placed into a container, ground into a powder, incubated in a container in a lysis solution containing proteinase K (0.5 mg/ml), treated with phenol/chloroform and ethanol which involved centrifugation to make a pellet and removal of supernatant containing DNA (limitations of Claim 1e, f, 24-26, 27). With respect to Claim 27 for separating short length fragments, the centrifugation would separate the fragments such that the smaller molecules would remaining in the supernatant. Meltzer then teaches that the method amplifies the isolated DNA by PCR and detects a mutation associated with the cancer, i.e. the loss of herterozygosity in the p53 region of chromosome 17 (page 4977, col. 1 and page 4978, col. 2)(limitations of Claim 1fg, h, 28-32, 35). With respect to Claim 23, the claim requires cutting an arc segment from the specimen. It is noted that using a cutting mechanism of Meltzer would not form a perfect section, thus, some extent of an arc would be present. Therefore, since Meltzer teaches every limitation recited in the claims, Meltzer anticipates the claimed invention.

Response to Arguments

The response states that the previously filed claims did not contain a step of centrifugation or supernatant removal. The response asserts the new claims are not anticipated by Meltzer. This argument has been reviewed but is not convincing because the claims are written using the comprising language and do not state that the centrifugation step is performed on the container without any additional extraction or lysis steps and because the 'centrifuging" step is not written such that only a single centrifugation step occurs to produce supernatant which is used for a CPR amplification step without additional extraction steps, the claims still read on the method of Meltzer.

The response asserts that the method of Meltzer requires DNA isolation by phenol/chloroform extraction. This argument has been thoroughly reviewed, but is not found persuasive because, as discussed above, the claim is broadly written to encompass the phenol/choloroform extraction step due to the use of the "comprising" language and because the method steps do not set forth that the separated piece of tissue is directly centrifuged to produce a supernatant which is directly added to a PCR reaction without extraction of the DNA.

Second, the response argues that Meltzer does not specifically state that single tissue section is sufficient for analysis and that Meltzer used tissue sections of 10 micron thickness. This argument has been thoroughly reviewed, but is not found persuasive because the claims do not require these limitations. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification,

limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Addition of these limitations would require further search and consideration.

Third, the response argues that the centrifugation step of Meltzer was in the context of centrifugation for phenol/chloroform separation. This argument has been thoroughly reviewed, but is not found persuasive because, as discussed above, the claims encompass such as step due to the use of comprising language and the breadth of the method steps. This step does not exclude addition of phenol/chloroform nor multiple centrifugation steps. Consequently, the claims read on the method of Meltzer.

It is noted that Meltzer does not perform a PCR reaction on supernatant obtained after centrifugation of the piece of separated tissue which has been placed in a container having lysis buffer. However, as noted above, the claims are not drawn to such a method. However, this method would not be allowable over the prior art because references such as Teramoto et al. (Acta Med. Okayam 1994 48(4): 189-193) teach that PCR has been used to directly amplify DNA which ahs been extracted from a separated piece of tissue by digestion in lysis buffer (page 190, col. 1, last para.) without phenol/chloroform to produce a supernatant containing DNA. This is the procedure described in the instant specification. Consequently, it would have been obvious to the ordinary artisan that the method of Meltzer could have been greatly simplified by eliminating the phenol/chloroform extraction step and instead amplifying the DNA directly from supernatant obtained after performing a proteinase based lysis step as taught by Teramoto. The ordinary artisan would have had a reasonable

expectation for success because Teramoto showed that PCR was able to amplify DNA directly from supernatant from a single cell. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meltzer et al (PNAS, Vol. 88, pages 4976-4980, June 1991) in view of Erlich (PCR Technology, 1990).

Meltzer et al. (herein referred to as Meltzer) teaches a method of detecting LOH using PCR. Meltzer modified the PCR reaction to enable detection of LOH using small

quantities of DNA obtained from microdissected frozen biopsies or archival paraffin sections (page 4976, col. 2). Meltzer teaches a genotyping method comprising obtaining a specimen of cells containing DNA and placing under a microscope, inspecting the cells to determine target cells, choosing target ells based on morphological features characteristic of a disease and separating the target cells (page 4976, col. 2, para 2) by teaching that cell samples were obtained from patients with esophageal cancer frozen in liquid nitrogen, embedded in paraffin and microdissected by placing the sample under the microscope and observing morphological differences between the tumor areas and normal cells (limitations of Claims 18 a, b, c, d, 19-22). Meltzer then teaches that the tumor cells were microdissected to separate them from adjacent normal cells to achieve an enrichment of about 70% or greater. Meltzer then places the separated piece into a container, centrifuging to make a pellet and withdrawing supernatant to obtain DNA (page 4976, col. 2, para 3) by teaching that the separated tissue was placed into a container, ground into a powder, incubated in a container in a lysis solution containing proteinase K (0.5 mg/ml), treated with phenol/chloroform and ethanol which involved centrifugation to make a pellet and removal of supernatant containing DNA (limitations of Claim 1e, f, 24-26, 27). With respect to Claim 27 for separating short length fragments, the centrifugation would separate the fragments such that the smaller molecules would remaining in the supernatant. Meltzer then teaches that the method amplifies the isolated DNA by PCR and detects a mutation associated with the cancer, i.e. the loss of herterozygosity in the

p53 region of chromosome 17 (page 4977, col. 1 and page 4978, col. 2)(limitations of Claim 1fg, h, 28-32, 35).

While Meltzer teaches using a temperature of 95 degrees (no greater than 99 degrees) and back to 57 (rather than 55) in 5 minutes, Meltzer does not specifically teach bringing the temperature back to 55 degrees.

However, Erlich teaches the "standard" reaction for PCR which is widely used. The amplification can be performed in a DNA Thermal Cycler suing the Step-Clycle program set to denature at 94 degrees (not more than 99 degrees) followed by annealing at 55 degrees for 20 seconds. Erlich teaches that the conditions can be used to amplify a wide range of target sequences with excellent specificity.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the PCR conditions of Meltzer with the "standard" protocol suggested by Erlich. Erlich teaches that the conditions can be used to amplify a wide range of target sequences with excellent specificity. Therefore, the skilled artisan would have been motivated to have tweaked the PCR conditions provided by Meltzer depending on the target sequence desired to amplify.

8. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meltzer et al (PNAS, Vol. 88, pages 4976-4980, June 1991) in view of Erlich (PCR Technology, 1990) in further view of Teramoto et al (Jpn. J. Cancer Res. Vol. 83, pages 329-333 April 1992).

Meltzer et al. (herein referred to as Meltzer) teaches a method of detecting LOH using PCR. Meltzer modified the PCR reaction to enable detection of LOH using small quantities of DNA obtained from microdissected frozen biopsies or archival paraffin sections (page 4976, col. 2). Meltzer teaches a genotyping method comprising obtaining a specimen of cells containing DNA and placing under a microscope, inspecting the cells to determine target cells, choosing target ells based on morphological features characteristic of a disease and separating the target cells (page 4976, col. 2, para 2) by teaching that cell samples were obtained from patients with esophageal cancer frozen in liquid nitrogen, embedded in paraffin and microdissected by placing the sample under the microscope and observing morphological differences between the tumor areas and normal cells (limitations of Claims 18 a, b, c, d, 19-22). Meltzer then teaches that the tumor cells were microdissected to separate them from adjacent normal cells to achieve an enrichment of about 70% or greater. Meltzer then places the separated piece into a container, centrifuging to make a pellet and withdrawing supernatant to obtain DNA (page 4976, col. 2, para 3) by teaching that the separated tissue was placed into a container, ground into a powder, incubated in a container in a lysis solution containing proteinase K (0.5 mg/ml), treated with phenol/chloroform and ethanol which involved centrifugation to make a pellet and removal of supernatant containing DNA (limitations of Claim 1e, f, 24-26, 27). With respect to Claim 27 for separating short length fragments, the centrifugation would separate the fragments such that the smaller molecules would remaining in the supernatant. Meltzer then teaches that the method amplifies the isolated DNA by PCR

and detects a mutation associated with the cancer, i.e. the loss of herterozygosity in the p53 region of chromosome 17 (page 4977, col. 1 and page 4978, col. 2)(limitations of Claim 1fg, h, 28-32, 35).

Meltzer does not specifically teach using section of paraffin sections which are between 2-6 um thick.

However, Teramoto teaches that for PCR of DNA obtained from microscopically identified cells, 6 um thick sections were used.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the paraffin sections used in the method of Meltzer with the smaller sections taught by Teramoto. Teramoto teaches PCR amplification may be performed on small sections of tissue. Therefore, the ordinary artisan would have been motivated to have used a smaller amount of sample either because of the limited amount of sample available or to preserve sample for subsequent analysis.

Conclusion

9. No claims allowable.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Liotta et al (US Pat. 5,83,644, December 1998)- Liotta teaches a method of direct extraction of cellular material from a tissue sample which uses a microscope, identification of a cell, extraction of cells and analysis.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
October 1, 2003

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER